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υπό

ΕΥΣΤΑΘΙΟΥ ΘΕΟΔΟΣΙΑΔΗ

Ειδικευόμενος Αναισθησιολογίας

Υπεβλήθη για την εκπλήρωση μέρους

των απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

«Θρόμβωση και Αντιθρομβωτική Αγωγή»

Λάρισα, 2022

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Τίτλος εργασίας στα αγγλικά:

Perioperative management of patients under antithrombotic therapy for metal heart valve undergoing non cardiac surgery

ΕΥΧΑΡΙΣΤΙΕΣ

Θα ήθελα να ευχαριστήσω την επιβλέπουσα μου, Καθηγήτρια κ. Ελένη Αρναούτογλου για τη σημαντική βοήθειά της

Επίσης τον Καθηγητή κ. Μιλτιάδη Ματσάγκα για το συγκεκριμένο μεταπτυχιακό

Τους διδάσκοντες του μεταπτυχιακού για τις άρτιες παρουσιάσεις τους

Την γραμματεία του μεταπτυχιακού για την άριστη οργάνωση και άμεση ανταπόκριση σε κάθε αίτημα

Τέλος ευχαριστώ τους γονείς μου που αποτελούν αρωγό σε κάθε προσπάθειά μου

Θεοδοσιάδης Ευστάθιος

Περίληψη

Ασθενείς με μεταλλικές καρδιακές βαλβίδες σε αρκετές περιπτώσεις, χρήζουν χειρουργικής επέμβασης σε προγραμματισμένη βάση. Οι ανταγωνιστές βιταμίνης Κ αποτελούν τη μοναδική επιλογή αντιθρομβωτικής αγωγής για τους ασθενείς με μεταλλική βαλβίδα. Ο κίνδυνος θρόμβωσης μιας μεταλλικής βαλβίδας κατά την περιεπεμβατική περίοδο είναι παράγοντας θνητότητας και νοσηρότητας. Για το λόγο αυτό είναι απαραίτητη η εξασφάλιση ισορροπίας μεταξύ θρόμβωσης και αιμορραγίας για τους ασθενείς αυτούς. Με τη συγκεκριμένη εργασία επιχειρείται η παρουσίαση των υπαρχόντων δεδομένων αναφορικά με την περιεγχειρητική διαχείριση των αντιπηκτικών παραγόντων στους ασθενείς αυτούς, οι οποίοι θα υποβληθούν σε μη καρδιοχειρουργική επέμβαση, καθώς και η αξιολόγηση της ασφάλειας και της αποτελεσματικότητας της γεφύρωσης της αντιπηκτικής αγωγής κατά την περιεπεμβατική περίοδο.

Λέξεις Κλειδιά:

Βαρφαρίνη, ανταγωνιστές βιταμίνης Κ, μεταλλικές βαλβίδες καρδιάς, μη καρδιοχειρουργικές επεμβάσεις, μικρού μοριακού βάρους ηπαρίνη, αιμορραγία

Abstract

Introduction: Patients with mechanical heart valves should often undergo planned surgical procedures. To date only vitamin K antagonists are approved for the prevention of thrombosis in patients with mechanical heart valves. The risk of perioperative thrombosis increases the morbidity and mortality of patients.

Objective: to present the current data on perioperative management of antithrombotic therapy for patients with mechanical heart valves who undergo non cardiac surgical procedures and to evaluate the safety and efficacy of perioperative bridging in patients with mechanical heart valves undergoing non-cardiac interventions.

Materials and Methods: A systematic research using Medline, EMBASE, and Google Scholar databases was implemented corresponding to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA). Data from the qualified studies were recovered and meta-analyzed. Primary endpoints included major bleeding and thromboembolism. Secondary endpoints included minor bleeding, overall mortality, and overall bleeding. A comparative analysis between bridging and non-bridging was conducted along with a sensitivity analysis for patients undergoing major and minor operations.

Results: Fifteen studies comprised of 2305 patients (2453 bridging episodes) were included. Pooled major bleeding and thromboembolism rates were 3.85% (95%CI:2.12-5.98) (I^2=69%, p<0.01) and 0.39% (95%CI:0.00-1.41) (I^2=64%, p<0.01) respectively. Bridging versus non-bridging major bleeding, thromboembolism, and overall bleeding risk ratios (RR) were RR 2.05 (95%CI:0.98-4.28) (I^2=10%, p=0.34), RR 1.63 (95%CI:0.41-6.50) (I^2=0%, p=0.63) and RR 1.79 (95%CI:1.17-2.72) (I^2=55%, p=0.09) respectively. Subgroup analysis displayed major and minor operation thromboembolism and overall bleeding rates of 3.09% (95%CI:0.78-6.43)

(I^2=0%, p=0.89) versus 0.14% (95%CI:0.00-1.40) (I^2=0%, p=0.93), test for subgroup differences (p<0.01) and 17.37% (95%CI:11.73-23.77) (I^2=0%, p=0.61) versus 28.18% (95%CI:22.80-33.88) (I^2=0%, p=0.47), test for subgroup differences (p=0.01) respectively.

Conclusion: Bridging puts patients at an increased bleeding risk while failing to provide statistically significant benefits concerning thromboembolism and overall mortality compared to patients undergoing anticoagulation interruption without bridging. Additionally, one in four patients having minor surgery under bridging therapy experiences a bleeding episode.

Key words:

Warfarin, vitamin K antagonists, metallic heart valves, non cardiac surgery, low molecular weight heparin, hemorrhage

Contents

Chapter 1

Introduction

With the increased availability of transcatheter heart valve treatment, mechanical heart valves (MHV) have mitigated key advantages over their biological counterparts such as their lifelong durability and the need for fewer re-operations. Nonetheless and despite substantial reduction in MHV use over the past two decades, about 48% of patients between the ages of 50 and 70 years in need for valvular surgery undergo mechanical heart valve implantation[1, 2].

The principal disadvantage of MHV is the necessity for life-long anticoagulation with oral anticoagulants (OAC), mostly vitamin K antagonists (VKA). OACs require regular monitoring and strict patient adherence to treatment protocols including self-managing of INR. An extension to this disadvantage is the dilemma arising for patients undergoing planned non-cardiac invasive procedures. Discontinuation of OACs puts patients at an increased risk for thrombotic events while the initiation of bridging therapy may potentially cause excessive bleeding.

According to the recently published guidelines by the European Society of Cardiology (ESC), patients with MHV undergoing minor surgical operations are advised against OAC interruption. On the contrary major surgical interventions require bridging therapy with either low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH), (class of recommendation: I). Additionally, the guidelines published by the American Heart Association/American College of Cardiology (AHA/ACC) also advise against VKA interruption prior to minor surgery (class of recommendation: I, level of evidence: C – Expert Opinion) while in the case of major surgery, bridging therapy is recommended for patients with a mechanical aortic valve replacement (AVR) and any thromboembolic risk factor, an older-generation mechanical AVR, or a mechanical mitral valve replacement, (class of recommendation:2a, level of evidence: C – Limited Data)[3, 4].

The bridging protocol proposed by the ESC, includes interruption of VKA five days prior to-and initiation of heparin therapy four days before the intervention. Heparin should be stopped six hours or one day before the operation depending on the pharmacological agent (six hours for UFH, 24 hours for therapeutic dose of LMWH and 12 hours for prophylactic dose of LMWH) while it is to be resumed 12 to 24

hours after the intervention with the addition of VKA. Heparin therapy is terminated approximately four days post-intervention depending on INR target values (INR>2.0 for aortic valve and INR>2.5 for mitral valve mechanical prostheses)[4]. Other recommended protocols follow roughly similar patterns.

Despite the recommendations about bridging practices published by a series of scientific societies, the lack of high-quality evidence nourish a perpetuating debate over the appropriateness of bridging therapy for patients with MHV undergoing either minor or major non-cardiac interventions.

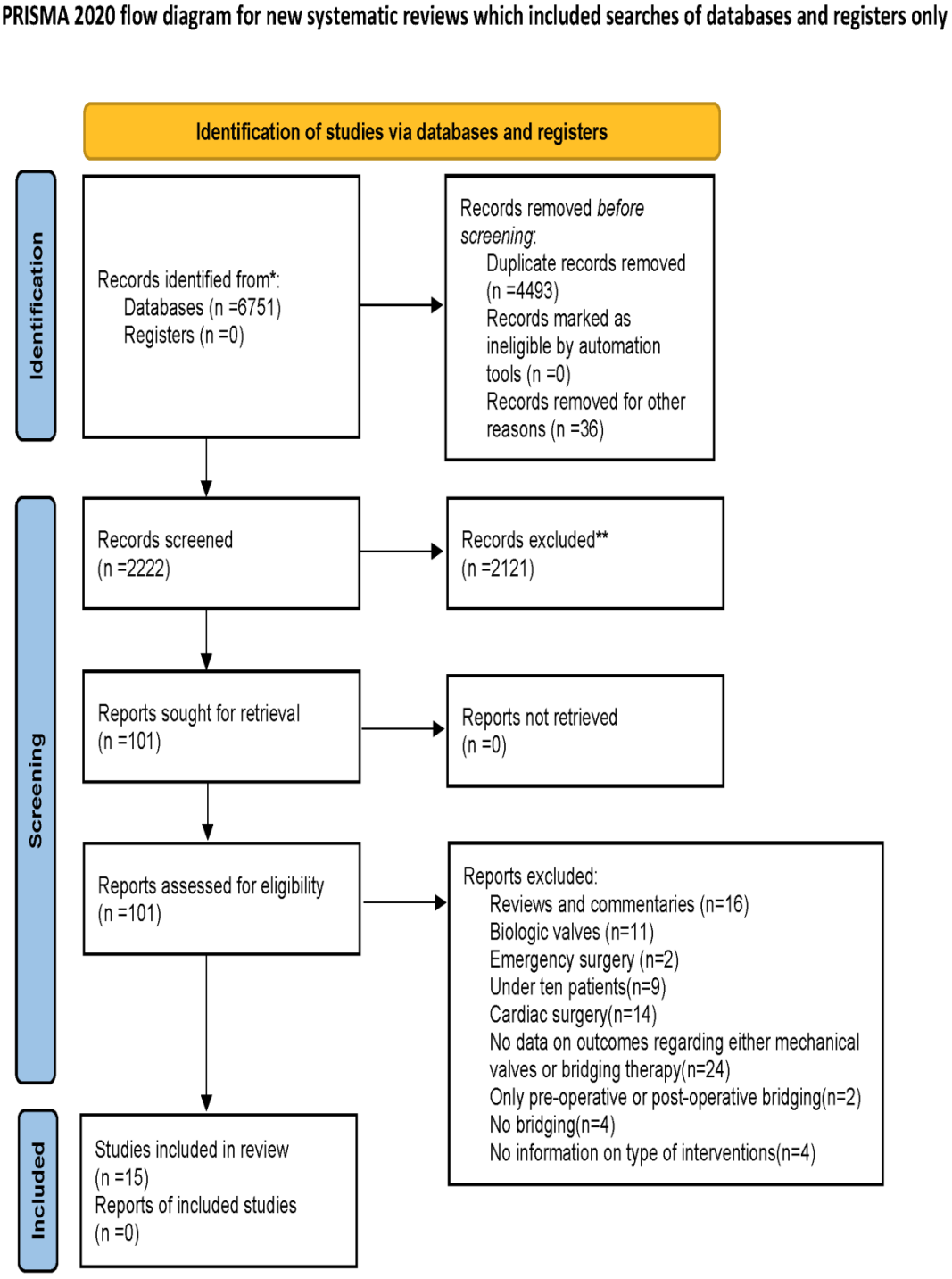
Chapter 2

Material and methods

2.1 Design

We conducted a systematic review in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The endpoints inclusion and exclusion criteria were established through an investigation protocol. The protocol is accessible upon inquiry.[5]. **(Figure 1)**

Figure 1. PRISMA flow diagram



2.2 **Inclusion and exclusion criteria**

Studies describing perioperative bridging in patients with mechanical heart valves undergoing non-cardiac interventions regardless of study design where included. Studies that did not include both pre-operative and post-operative bridging of Vitamin K antagonist with either LMWH or UFH were excluded. Studies that reported exclusively on cardiac surgery procedures including any form of open-heart surgery (e.g., coronary artery bypass, valve placement surgery) or coronary artery angioplasty and stenting were excluded. Studies that reported on mixed cardiac and non-cardiac interventions were included in the cases where patients undergoing cardiac-interventions could be excluded from the analysis or if cardiac surgery population in the study was under 5% of the total study population and none of the events under investigation occurred in cardiac-surgery patients. Studies with a patient population of under ten patients were excluded.

2.3 Information sources and search strategy

A systematic research was performed on Medline, EMBASE, and Google Scholar for reports published by July 2022. The terms used included: “mechanical heart valves”, “bridging therapy” and “mechanical valve bridging”. There were no language or demographic limitations.

2.4 Quality assessment of the included studies

Appraisal of the quality of the included studies was regulated conforming to the Methodological Index for Non-Randomized Studies (MINORS). Non-comparative studies were scored as 0-8 low, 9-12, moderate and 13-16 high quality respectively. Evaluation of comparative studies was determined as 0-12 low, 13-18 moderate and 19-24 high quality. The intraclass correlation coefficient (ICC) was applied to ascertain inter-observer quality agreement[6].

2.5 Endpoints

Primary endpoints consisted of major bleeding and thromboembolism. Secondary endpoints included minor bleeding, overall mortality, and overall bleeding.

Chapter 3

3.1 Definitions

As major bleeding was defined any clinically overt bleeding resulting in death, transfusion, reoperation, hospitalization, or admission to the emergency department occurring the immediate post-operative period. Minor bleeding was defined as any other clinically apparent bleeding. Overall bleeding was defined as the summary of major and minor bleeding events. Thromboembolism was defined as cardiac valvular or mural thrombus confirmed by transthoracic or transesophageal echocardiography, any incident of stroke, transient ischemic attack (TIA) or an embolus documented operatively, at autopsy, clinically or using imaging modalities producing symptoms attributable to complete or partial obstruction of an artery. Overall mortality was defined as any documented incident of death the immediate post-operative period attributed to the procedure or perioperative management. As major operations were defined any major abdominal/thoracic/gynecologic surgery, as well as all vascular, urologic, and neurosurgical interventions. Studies where 70% or more of patients underwent major operations were included in the major operation subgroup. As minor surgeries were defined any dental, dermatologic, ear, nose, and throat (ENT) interventions, minor abdominal, thoracic, and gynecological surgery, any non-coronary minimally invasive cardiologic interventions such as defibrillator/pacemaker implantation and coronary angiography without angioplasty as well as gastrointestinal endoscopic procedures such as colonoscopy and gastroscopy. Studies where 10% or less of the total number of operations were categorized as minor were included in the minor operations subgroup.

3.2 Effect measures and synthesis methods

The effect estimates were calculated applying the back-transformation of the inverse variance weighted means utilizing the Freeman-Tukey Double arcsine transformation. The Der Simonian and Laird method was employed for the calculation of between study variances for Random effects meta-analysis and the Restricted Maximum Likelihood method for the calculation of between study variances for Fixed effects meta-analysis. The confidence intervals of a mean were calculated using the normal approximation. Outcomes are reports as proportions (%) with their corresponding 95% confidence intervals (CI). Log relative risks (RR) were generated by the Mantel-Haenszel method using the Paule-Mandel variance estimator, back-transformed and presented as RR with their corresponding 95% CI. A sensitivity analysis was performed between studies describing patients undergoing major and minor surgical interventions. Heterogeneity was tested implementing the I^2. Meta-analytic processes were performed with the use of R (R Foundation for Statistical Computing, Vienna, Austria, v 4.1.0).

Chapter 4

4.1 Baseline study characteristics

Fifteen studies, one RCT, four prospective case series and ten retrospective case series including 2305 patients and 2453 bridging episodes were included[7-21]. Eleven studies reported on mechanical valve anatomic locations with 56% (1218/2178) of the patients having aortic valves, 35.8% (779/2178) mitral valves, 0.05% tricuspid valves (1/2178) and 8.3% (180/2178) multiple mechanical valves[7, 9-11, 13, 15, 18-21]. Bridging was conducted using LMWH in nine studies[8, 10-13, 15, 16, 18, 20], UFH in one study[19], while five studies used both medications for bridging[7, 9, 14, 17, 21].Twelve studies reported on the type of interventions with 50.3% (590/1172) of the interventions being defined as major operations[7, 9-12, 14-19, 21]. Ten studies reported extractable data on bridging with either therapeutic or prophylactic doses of heparin with 82% (1170/1427) of bridging episodes being conducted according to therapeutic protocols[8, 9, 11, 12, 15, 16, 18-21]. Fourteen studies reported on follow-up duration with a mean follow-up of 1.7 months. (**Table 1 – Baseline study characteristics**)

Table 1

	Study	Type	Total patients (n)	Total procedures (n)	Men (n)	Valve location (n)			
						AORTIC	MITRAL	MULTIPLE	TRICUSPID
1	Delate 2017	RCCS	547	547	339	303	181	62	1
2	Hjellström 2018	RCS	130	231	84	93	37	0	0
3	Daniels 2009	RCCS	556	580	377	372	136	48	0
4	Bitekcr 2012	PCS	140	140	73	77	46	17	0
5	Hammerstingl 2007	PCS	108	108	–	76	31	9	0
6	Kovacs 2004	PCS	112	113	75	–	–	–	–
7	Kovacs 2021	RCT	304	304	163	172	133	0	0
8	Ahmed 2010	RCS	11	11	–	–	–	–	–
9	Breen 2016	RCS	29	29	–	15	14	0	0
10	Bui 2009	RCS	32	54	–	–	–	–	–
11	Iqbal 2011	RCS	23	23	15	–	–	–	–
12	Han 2013	RCCS	98	98	52	10	54	33	0
13	Marquie 2006	RCS	38	38	17	21	8	9	0
14	Tinmouth 2001	PCS	12	12	–	7	3	2	0
15	Won 2014	RCCS	165	165	57	72	136	–	–

Type of anticaogulation	Type of bridging		Mean follow-up (months)	Procedure /Patient risk stratification		
	DRUG	Prophylactic/ Therapeutic		High	Moderate	Low
Warfarin	LMWH/UFH (unspecified)	N/A	1	289	185	73
Warfarin	LMWH	Prophylactic	1	49	_	_
Warfarin	LMWH (243)/UFH(99)	Theurapeutic	3	_	_	_
Warfarin	Enoxaparin	_	3	_	_	_
Phenprocoumon	Enoxaparin	Theurapeutic	1	23	_	64
Warfarin	Dalteparin	14.3%/76.8%	3	112	0	0
Warfarin	Dalteparin	Both (unable to extract data)	3	_	_	_
Warfarin	LMWH/UFH (unspecified)	_	1,5	_	_	_
Warfarin	Enoxaparin	Theurapeutic	1	23	6	0
Warfarin	Enoxaparin	Theurapeutic	2	54	0	0
Warfarin	LMWH/UFH	Both (unable to extract data)	1	_	_	_
Warfarin	LMWH	Theurapeutic	Perioperative	_	_	_
Fluindione,Acenocoumarol,Phenindione,	UFH	Theurapeutic	1	_	_	_
Warfarin	Dalteparin	Theurapeutic	1	_	_	_
Warfarin	LMWH (90)/UFH (75)	Theurapeutic	1	51	114	0

TYPE OF PROCEDURE						
Dental	ENT	EYE	Dermatologic	Gastrointestinal/ Endoscopy	Major Abdomina/Thoracic/Gynecologic	Minor Abdomina/Thoracic/Gynecologic
16	19	0	30	244	20	37
–	–	–	–	–	–	–
54	8	20	0	111	82	39
0	3	0	0	0	71	0
4	0	2	4	24	9	4
12	0	8	13	11	2	0
–	–	–	–	–	–	–
–	–	–	–	–	–	–
0	0	0	0	0	29	0
0	0	0	0	22	12	11
0	0	0	0	0	23	0
0	0	0	0	0	0	0
0	0	0	0	0	0	0
–	–	–	–	–	–	–
165	0	0	0	0	0	0

Orthopedic	Vascular	Urologic	Neurosurgery/Spinal	Pacemaker/Defibrilator/ Coronary angiography
63	34	22	24	15
–	–	–	–	–
60	20	17	9	75
25	0	26	5	0
0	0	0	2	55
10	0	20	0	19
–	–	–	–	–
–	–	–	–	11
0	0	0	0	0
5	0	0	0	0
0	0	0	0	0
0	0	0	0	98
0	0	0	0	38
–	–	–	–	–
0	0	0	0	0

4.2 Meta-analysis of included studies

Twelve studies reported on major bleeding rates [7-14, 17-19, 21]. The crude and pooled major bleeding rates were 4.53% (83/1831) and 3.85% (95%CI:2.12-5.98) (I^2=69%, p<0.01) respectively. Four studies provided major bleeding rates for patients undergoing bridging versus patients not undergoing bridging with a RR of 2.05 (95%CI:0.98-4.28) (I^2=10%, p=0.34)[7, 9, 13, 18]. **(Figure 2) (Figure 3)**

Figure 2. Major bleeding forest plot - Random effects model

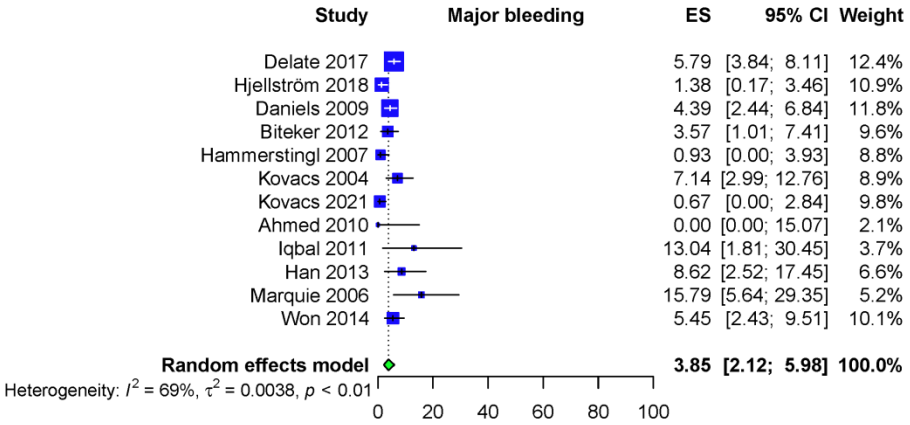
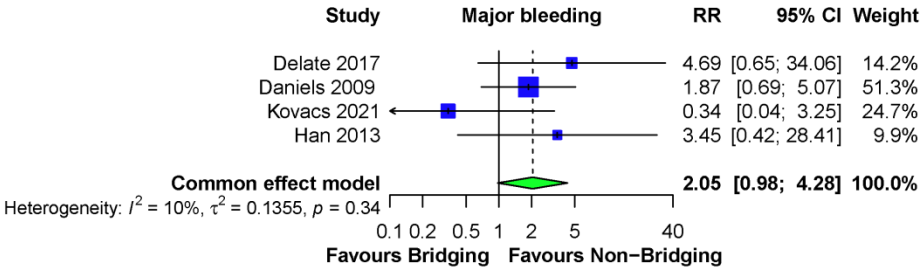


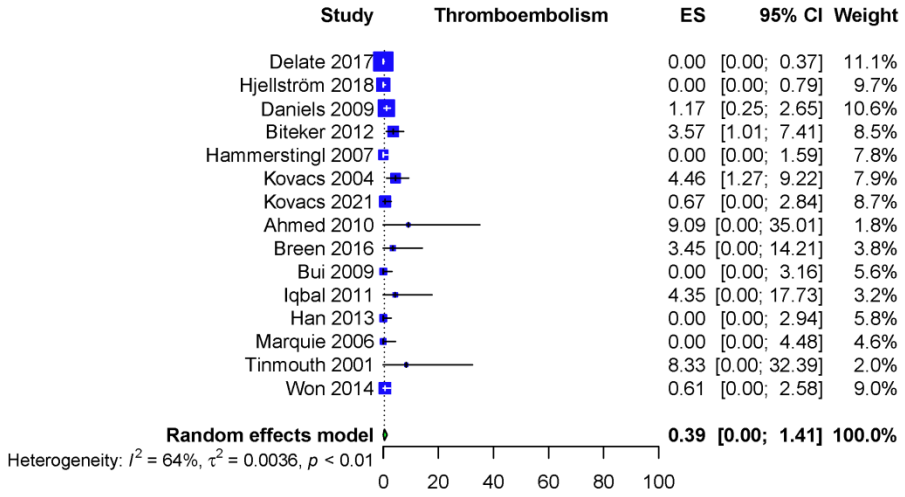
Figure 3. Major bleeding risk ratio (RR) – Fixed effects model



Subgroup analysis included two studies in the major operation group[10, 17], and three studies in the minor operation subgroup[18, 19, 21]. The mean MINORS score for the included studies in the subgroup analysis is 8.2 (SD=2.1) The rates for the subgroups were 3.96% (95%CI:1.19-7.88) (I^2=66%, p=0.08) and 7.12% (95%CI:4.16-10.71 (I^2=53%, p=0.12) each, test for subgroup differences (p=0.25).

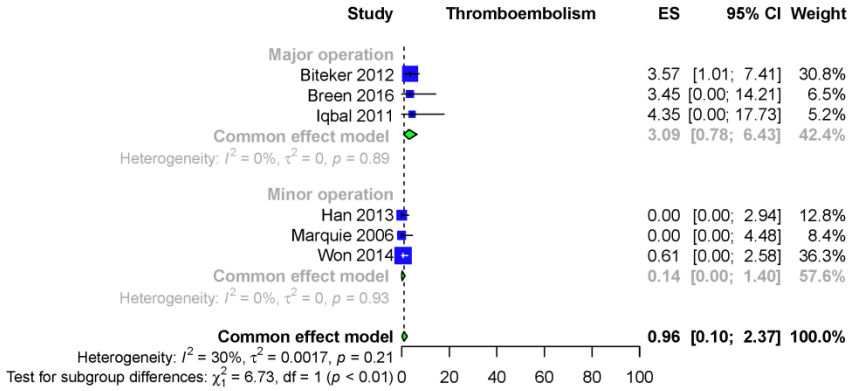
Fifteen studies reported on thromboembolic events. The crude and pooled thromboembolism rates were 1.03% (20/1926) and 0.39% (95%CI:0.00-1.41) (I^2=64%, p<0.01). **(Figure 4)**

Figure 4. Forest plot Thromboembolism Random effects model



Four studies compared bridging and non-bridging thromboembolisms with a RR of 1.63 (95%CI:0.41-6.50) (I^2=0%, p=0.63)[7, 9, 13, 18]. Subgroup analysis included three studies reporting on major operations group thromboembolic outcomes[10, 15, 17], and three studies in the minor operation subgroup[18, 19, 21]. The mean MINORS score for the included studies in the subgroup analysis is 8.7 (SD=2.2). The pooled rates for the two subgroups were 3.09% (95%CI:0.78-6.43) (I^2=0%, p=0.89) for major operations and 0.14% (95%CI:0.00-1.40) (I^2=0%, p=0.93) for minor operations, test for subgroup differences (p<0.01). **(Figure 5)**

Figure 5. Forest plot Thromboembolism sensitivity analysis Major versus Minor surgery – Fixed effects model



Twelve studies were included in the overall bleeding rate endpoint[7-14, 17-19, 21]. The crude and pooled overall bleeding rates were 10.87% (199/1831) and 12.62 % (95%CI:7.48-18.78) (I^2=91%, p<0.01) each. Four studies including 1504 patients reported on overall bleeding rates amongst the bridging and non-bridging populations with a RR of 1.79 (95%CI:1.17-2.72) (I^2=55%, p=0.09) favouring the non-bridging regimen. Subgroup analysis included two studies reporting on major operation group overall bleeding outcomes[10, 17], and three studies in the minor operation subgroup[18, 19, 21]. The mean MINORS score for the included studies in the subgroup analysis is 8.7 (SD=2.2). The pooled rates for the two subgroups were 17.37% (95%CI:11.73-23.77) (I^2=0%, p=0.61) for major operations and 28.18% (95%CI:22.80-33.88) (I^2=0%, p=0.47) for minor operations, test for subgroup differences (p=0.01).

(Figure 6) (Figure 7)

Figure 6. Forest plot overall Bleeding Bridging vs no bridging Fixed effects model

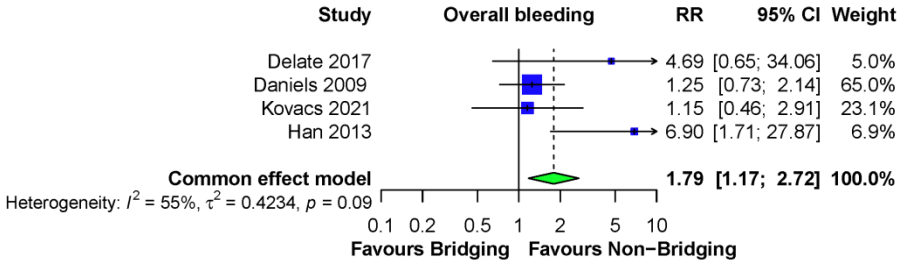
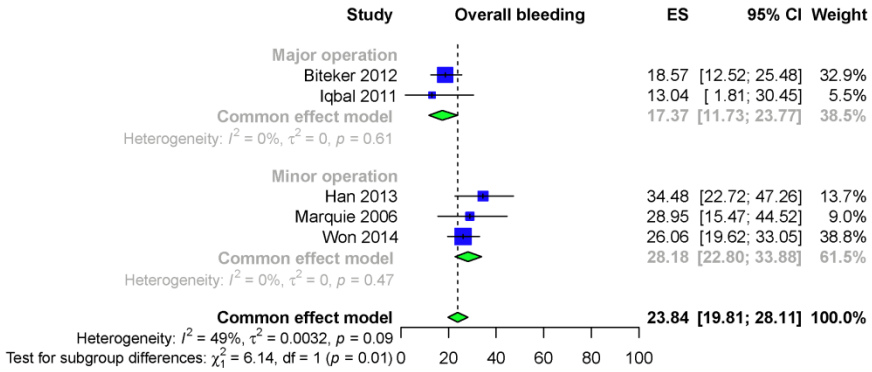


Figure 7. Sensitivity analysis Forest plot Overall bleeding Major vs Minor surgery Fixed effects model



Minor bleeding was reported by eight studies[9-11, 13, 14, 18, 19, 21]. The crude and pooled minor bleed rates were 11.46% (116/1012) and 12.46 % (95%CI:7.35-18.57) (I^2=83%, p<0.01). Three studies including 957 patients compared minor bleeding incidents in the bridging and the non-bridging groups with a RR of RR of 1.65 (95%CI:0.98-2.78) (I^2= 59%, p= 0.09)[9, 13, 18]. Only one study belonging to the major surgery group reported on minor bleeding outcomes rendering subgroup analysis unavailing.

Overall mortality was reported by ten studies[7, 8, 10, 12, 13, 15-17, 19, 21]. The crude and pooled overall mortality rates were 0.43% (6/1395) and 0.02% (95%CI:0.00-0.33) (I^2=11%, p=0.34) respectively. Comparative outcomes on mortality rates were reported by two studies making further statistical analysis inapt. Sensitivity analysis included three studies reporting on major operations group overall mortality rates [10, 15, 17], and two studies in the minor operation subgroup[19, 21]. The pooled rates for the two subgroups were 0.45% (95%CI:0.00-2.51) (I^2=0%, p=0.90) and 0.61 % (95%CI:0.00-2.55) (I^2=21%, p=0.26) respectively, test for subgroup differences (p=0.90).

Chapter 5

Discussion

Major and minor bleeding rates did not display significant variations, neither among bridging and non-bridging nor between major and minor operation subgroups. Thromboembolic events, on the contrary, occurred at a larger pace in the major operation subgroup compared to minor operations (3.09% versus 0.14%). Patients undergoing bridging therapy experienced a 79% increased risk for overall bleeding complication occurrence compared to non-bridging. Additionally, a significantly increased overall bleeding rate for patients undergoing minor operations under bridging compared to patients in the major operation subgroup was identified (28.18% versus 17.37%). Overall mortality rates in the study were minimal without significant differences among subgroups.

Periprocedural management of chronically anticoagulated patients is a routinely encountered clinical problem. The uncertainty around bridging strategies is present since the early years of VKA use. The debate around bridging is driven by the fear of thrombotic events on the one hand and hemorrhagic complications on the other hand, potentially threatening patients following either bridging or non-bridging regimens. According to several published guidelines, the equilibrium between thrombosis and hemorrhage is achieved through patient and procedural risk assessment, often requiring a multidisciplinary approach.

The reported annual thromboembolic and hemorrhagic complications risk rates for patients with a history of mechanical valve replacement under OAC, vary widely with reported rates ranging from 0.7% to 6% for thromboembolic events and 0.34% to 2.91% for hemorrhagic complications[22, 23]. To date, high-quality studies investigating the role of bridging in surgical scenarios are limited to atrial fibrillation (AF) patients. The BRIDGE trial investigating perioperative warfarin interruption and bridging with prophylactic doses of LMWH in patients with AF, reported thirty day thromboembolic and major hemorrhage rates of 0.3% and 3.2% respectively while it displayed the non-inferiority of non-bridging therapy to bridging [24].

Results from the recently published PERIOP2 study, (included in the analysis) a study where both prophylactic and therapeutic doses of LMWH were used in a mixed AF and MHV population displayed a 90-day thromboembolic rate of 1% and a

major bleeding rate of 1.3%, while it too failed to showcase the benefit of bridging therapy. In the present review, at a mean follow-up of 1.7 months, the pooled thromboembolic event rate was 0.39% while the major bleeding rate was 3.85%. The increased bleeding rates that were displayed compared to both RCTs could be attributed to the differences in heparin dosing since the vast majority of bridging episodes in the present review were undertaken with the use of therapeutic doses of heparin.

Like the BRIDGE and PERIOP2 studies, it was also unable to be showcased the beneficial effect of bridging therapy on thromboembolism prevention for patients undergoing non-cardiac interventions. On the contrary, patients treated under a bridging protocol faced a borderline statistically insignificant risk for major bleeding complications and an almost 80% statistically significant risk for overall hemorrhagic complications (major and minor). Nonetheless, these results should be interpreted with cautions since the comparative analysis is based on weak evidence because of various limitations presented by the included studies. Initially, the moderate quality of included studies in addition to the mixed major and minor surgery population involved in the analysis (51% undergoing major operation), cannot allow for proper evaluation of the results in conjunction to published guidelines where they suggest bridging therapy exclusively for patients undergoing major surgical operations. Additionally, two of the four included studies in the comparative analysis used both LMWH and UFH with two studies following a therapeutic dose protocol, one study both therapeutic and prophylactic regimens, while one study failed to provide dose specifications.

Subgroup analysis between studies included in the major and minor operation subgroups displayed statistically significant differences in both thromboembolic events and overall bleeding rates. Once again and despite the increased incident of major hemorrhagic events displayed between the major and minor operation groups (3.96% and 7.12%) the result was not statistically significant.

Regarding overall bleeding rates, one would expect major operations to result in higher bleeding rates compared to minor operations. The statistically significant difference in overall bleeding rates between the two subgroups could be largely attributed to variations in surgical settings between the two types of procedures. Often minor surgeries are performed on an outpatient basis (dental tooth extraction, skin biopsies) by non-surgeons, lacking the knowledge and the appropriate equipment to

provide adequate hemostasis. On the contrary, major operations are performed by trained physicians possessing both the knowledge and the equipment (electrocautery, hemostatic dressing) to perform hemostasis. Additionally, all three included studies in the minor surgery subgroup performed bridging with the use of therapeutic LMWH doses. Regarding thromboembolic events, patients in the major operation group experienced an event rate of 3.09% compared to 0.14% for the minor surgery group suggesting a minimal risk for thromboembolic phenomena for patients undergoing minor procedures and an increased risk for patients undergoing major interventions potentially justifying the use of bridging for this particular group of patients. These findings are in line with ESC guidelines suggesting that roughly one in four patients undergoing minor surgery under bridging therapy with therapeutic LMWH will experience a bleeding episode. The role of prophylactic LMWH bridging therapy in minor surgery and the ideal strategy (interruption without bridging or continuation of VKA) should be the subject of further research.

Conclusions

It was showcased that bridging therapy puts patients at an increased bleeding risk while failing to provide statistically significant benefits regarding thromboembolic events and overall mortality compared to patients undergoing simple OAC interruption. Additionally, it was displayed that roughly one in four patients undergoing minor surgery under bridging therapy will experience a bleeding episode. Further investigation through high quality comparative studies is warranted to investigate the overall role of bridging therapy in non-cardiac surgery and the appropriate dose regimens.

MINORS

Table 2

	Delate 2017		Hjellström 2018		Daniels 2009	
	Person A	Person B	Person A	Person B	Person A	Person B
A clearly stated aim	2	2	2	2	2	2
Inclusion of consecutive patients	2	1	1	2	2	2
Prospective collection of data	1	1	1	1	1	1
Endpoints appropriate to the aim of the study	2	2	2	2	2	1
Unbiased assessment of the study endpoint (blind)	0	0	0	0	2	2
Follow-up period appropriate to the aim of the stud	2	2	2	2	2	2
Loss to follow-up less than 5%	0	2	0	0	2	2
Prospective calculation of the study size	0	0	0	0	0	0
Adequate control group	2	2				
Contemporary groups	2	2				
Baseline equivalence of groups	2	1				
Adequate statistical analyses	2	2				

Biteker 2012		Hammerstingl 2007		Kovacs 2004		Kovacs 2021		Ahmed 2010		Breen 2016		Bui 2009	
Person A	Person B	Person A	Person B	Person A	Person B	Person A	Person B	Person A	Person B	Person A	Person B	Person A	Person B
2	2	2	2	2	2	2	2	2	2	1	1	2	2
2	2	2	2	2	2	2	2	2	1	0	0	0	1
2	2	2	2	2	2	2	2	1	1	1	1	1	1
2	2	2	2	2	2	2	2	2	2	1	0	2	2
0	0	0	0	0	0	2	2	0	0	0	0	0	0
2	2	2	2	2	2	2	2	2	2	2	2	2	2
0	2	0	0	2	1	2	2	0	0	0	0	0	0
0	0	0	0	0	0	2	2	0	0	0	0	1	0
						2	1	2	1				
						1	2	1	1				
						2	2	2	1				
						2	2	2	2				

Iqbal 2011		Han 2013		Marquie 2006		Tinmouth 2001		Won 2014	
Person A	Person B	Person A	Person B	Person A	Person B	Person A	Person B	Person A	Person B
2	2	2	2	2	2	2	2	2	2
0	1	2	2	0	1	2	2	2	2
1	1	1	1	1	1	2	2	2	1
2	2	2	2	2	2	2	1	1	2
1	0	0	0	0	0	0	0	0	0
2	2	2	2	2	2	2	2	2	2
0	0	0	0	2	1	2	0	0	2
1	0	0	0	0	0	0	0	0	0
		2	1						
		2	2						
		2	2						
		2	2						

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